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EVALUATION OF TESTS USED IN THE DIAGNOSIS OF PHEOCHROMOCYTOMA*

PART II

In a previous communication an evaluation was made of those drugs giving a positive test for the diagnosis of pheochromocytoma which cause a pressor response and which are to be used preferably at a time when the control blood pressure is at or near normotensive levels.[1] We now propose to discuss the present status of the pharmacological agents which indicate a positive test for pheochromocytoma by inducing a depressor response. These drugs consist of benzodioxane, dibenamine, and, the more recently employed agent, regitine. These tests are to be used in those patients whose blood pressures are elevated to hypertensive levels. Tests in which measurements are made of the epinephrine and nor-epinephrine content in the urine and blood are included in this review.

Benzodioxane Test

Benzodioxane (933F) was first used as a test for the presence of pheochromocytoma by Goldenberg, Snyder, and Aranow[2] in 1947. They were able to establish the diagnosis of pheochromocytoma in four patients with persistent hypertension by noting a significant fall in the blood pressure in response to the intravenous injection of benzodioxane. These workers found that pheochromocytomas contained both epinephrine and nor-epinephrine in varying proportions. One tumor was found to contain as much as 97 per cent nor-epinephrine and 3 per cent epinephrine while, at the other extreme, another tumor contained only 14 per cent nor-epinephrine and 86 per cent epinephrine. It was maintained that the liberation of these pressor amines were responsible for the hypertension in pheochromocytoma. It was demonstrated that benzodioxane effectively blocked the pressor response of both epinephrine and nor-epinephrine.[3] The exact mechanism by which benzodioxane blocks epinephrine and nor-epinephrine as well as the reason why its administration may be associated with a pressor response in patients with essential hypertension remain obscure.

Test Procedure.

The same standard conditions for recording the blood pressure are maintained as for the histamine test. A 5 per cent solution of glucose in water is started intravenously. When the resting blood pressure has stabilized, benzodioxane should be injected over a 2-minute period through a 3-way stop-cock attached to the intravenous infusion. For adults, a dosage of 0.25 mg. per kilogram of body weight up to a maximum total dosage of 20 mg., is recommended. Following its administration, the blood pressure is recorded every 30 seconds for 5 minutes and thereafter every minute for 15 minutes.

The test is to be used in suspected cases of pheochromocytoma with sustained hypertension. Patients with uremia should not be subjected to the test since there is a high incidence of false positive tests where this complication is present.[4,5] No sedatives or narcotics of any kind should be used for 24 hours prior to the test as they are thought to be responsible for false positive reactions.[4]

The criteria for a positive test is a significant depressor response in which the systolic blood pressure falls 30 mm. or more and the diastolic pressure falls 30 mm. or more, within a time range to be mentioned presently.

Since 1949 we have found in the literature 22 cases of proven pheochromocytoma in which the benzodioxane test has been adequately reported. In this series there were unequivocally positive results in 15 patients, equivocally positive results in 4 patients[6,7,8,9] and false negative results in 3 cases.[8,10,11]

In the tests showing an unequivocally positive result, the depressor response consisted of a fall of 30 mm. or more in both the systolic and diastolic blood pressure, the maximum fall occurring prompty within 1 to 4 minutes after the start of the

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injection of benzodioxane. In 12 cases in which the time for the blood pressure to return to the resting control level was noted, this interval varied from 5 to 15 minutes in 9 cases, was 60 minutes in 2 cases, and was 90 minutes in one case. The average of the maximum depressor responses in the 15 unequivocally positive cases was 63/51.

The 4 equivocally positive results reported by Pitcairn,[6] Wilson,[7] Mason,[8] and Tulloh[9] deserve comment. In all these 4 cases the standard dosage and technique were used, and the timing and duration of the maximum responses were consistent with those seen in the tests giving unequivocally positive results. In Mason's case, the resting control level was 180/95 and the maximum depressor response was 50/15. The low diastolic depressor response may be attributed to the fact that the control diastolic pressure was only 95 mm. In analyzing the depressor responses in these 4 cases (26/38, 40/20, 50/15, and 40/0), we find that in each case, the fall in either the systolic or diastolic pressure was greater than 35 mm. Possibly, therefore, a depressor response exceeding 35 mm. in either the systolic or diastolic pressure should make one very suspicious of the presence of pheochromocytoma.

False negative tests have been reported in 3 patients by Wilkins,[10] Mason,[8] and Conley.[11] No apparent explanation for the failure of the test in these cases exists. It has been suggested that the dosage of benzodioxane used might not have been adequate, that some pressor substance other than epinephrine or nor-epinephrine might have been responsible for the hypertension, or that hypertension, once established, may persist even when the initial stimulus is inhibited. That the latter two speculations are not supported by facts is evident from the reports that all three of the false negative cases had a prompt and maintained relief from hypertension following removal of the pheochromocytoma.

The question of false positive benzodioxane tests has been investigated in detail. All 73 patients in Wilkins series[10] were operated upon. The adrenals were visualized and no tumors found. Sixty per cent gave a pressor response, 16 per cent showed no change in blood pressure, and 23 per cent had a mild depressor response, that is, less than 26/20, followed by a mild pressor effect. Other workers including Koffler,[12] Gifford,[4] Goldenburg,[2] Shapiro,[13] and Calkins[14] noted either a mild or no depressor response to benzodioxane in their cases. Emlet[5] in 62 patients with hypertension but without uremia found that the benzodioxane test gave a pressor response in 71 per cent, no change in blood pressure in 19 per cent, and a depressor response not exceeding 20/10 in 10 per cent. This same author then performed the test in 11 hypertensive patients with uremia whose NPN values in the blood averaged 57 mg. per cent. False positive tests were obtained in 5 of the patients. It is worthy of note that NPN levels in these 5 patients tended to be very high and that 3 of the patients were in various stages of confusion at the time of the test. Conley[11] has published a report of a false positive result in a hypertensive patient in whom no tumor was found at autopsy. The fact that the maximum fall in blood pressure was obtained 15 minutes after injection raises the question as to whether this should have been regarded as a false positive test. Soffer's case,[15] giving a false positive test and revealing no pheochromocytoma at autopsy, had a blood urea nitrogen of 82 mg. per cent and was comatose at the time of the test. This report emphasizes again the importance of taking into account nitrogen retention and the state of the patient in the interpretation of the benzodioxane test.

Mild side reactions such as flushing, palpitation, and throbbing in the head are to be expected following benzodioxane administration. Wilkins[10] noted this in 25 per cent of 73 hypertensive patients. He also observed in this same series a 4 per cent incidence of dizziness, oppressive feeling in the chest, and numbness in the extremities. More alarming has been the striking increase in blood pressure with systolic pressure going nearly to 300 mm. or higher and the diastolic pressure as high as 160 mm. reported in 10 patients with essential hypertension.[10,16,17] Fortunately, no permanent vascular damage resulted from these incidents although one of Bierman's cases went into pulmonary edema.[17] We have ready at the time of the test, hydergin as an antidote for a marked pressor effect.

Regitine Test

Emlet, Grimson and Bell,[5] and Gifford, Roth and Kvale[4] have been responsible for recently standardizing the regitine test as a diagnostic procedure for the presence of pheochromocytoma. No sedatives or narcotics of any kind should be given for 24 hours before the test. Regitine blocks the pressor effects resulting from infusions of both epinephrine and nor-epinephrine in dogs. It has been used in controlling the hypertensive crises of patients undergoing surgery for the removal of pheochromocytoma. The agent is to be given instantaneously by the intravenous route in a dosage of 5 mg. Higher dosages may give false positive results.

Gifford et al[4] reported their experience with the use of this test in 4 patients subsequently proven to have pheochromocytoma and in 107 hypertensive patients presumably without pheochromocytoma. The criteria for a positive result is a fall in systolic pressure exceeding 35 mm. and a fall in the diastolic pressure exceeding 25 mm. The occurrence of the maximum depressor effect was noted to take place within two minutes of the intravenous injection. We have no data on the duration of the depressor response that is consistent with a positive result. Three out of four of Gifford's patients with pheochromocytoma gave a positive response. A false negative result was obtained in the fourth case. It will be noted in this instance

that the resting control diastolic pressure was only 104 mm. Some depressor effect, usually less than 35 mm. systolic and 25 mm. diastolic, was observed in 66 per cent of the series of 107 hypertensive patients. There was a false positive reaction, i.e., a depressor response greater than 35/25, in 4 patients. Two of these 4 patients were heavily sedated at the time of the test and thorough abdominal exploration failed to reveal the presence of pheochromocytoma. One patient had terminal nephritis with a blood urea nitrogen value of 250 mg. per cent. Autopsy revealed chronic glomerulonephritis but no evidence of pheochromocytoma. One of these false positive tests remains unexplained. Experiences of Emlet et al with this test have not been included because they used the intramuscular route which gives erratic and unreliable results.

Regitine is a safe drug to use in that it is free of unpleasant side reactions and does not produce the alarming rise in blood pressure sometimes noted after benzodioxane administration. Adequate evaluation of regitine will have to await further experience with its use. In view of the limited number of reports on the use of this agent, it is recommended that all positive results be checked with the benzodioxane test and, if feasible, with the histamine test as well.

Dibenamine Test

The use of the dibenamine test for the diagnosis of pheochromocytoma in patients with sustained hypertension was suggested and the method described by Spear and Griswold[18] in 1948. A marked depressor response is claimed to constitute a positive test for pheochromocytoma.

In 7 cases with proven pheochromocytoma collected from the literature in which the dibenamine test was used, the test gave a positive response in every instance, the average fall in systolic pressure being 115 mm. and the average fall in diastolic pressure, 81 mm. Unfortunately, for purposes of differential diagnosis, dibenamine caused a maximum average depressor response of 59/38 mm. in all 14 patients with hypertension reported by Wunsch et al,[19] a fall to normotensive levels in 7 out of 20 hypertensive patients studied by Haimovici and Medinets.[20] Since a marked depressor response occurs with a high frequency in hypertensive patients without pheochromocytoma, the test is of very doubtful reliability in the diagnosis of pheochromocytoma.

Measurements of Epinephrine and Nor-Epinephrine in the Urine and Blood

Since epinephrine and nor-epinephrine were found to occur normally in the urine, it became a question of great interest whether an increased output of pressor amines could be demonstrated in cases of hypertension with or without pheochromocytoma. In all 6 patients with hypertension and pheochromocytoma proven at operation, there was a 10 to 50 fold increase in the daily urinary excretion of nor-epinephrine and epinephrine.[21] After removal of the tumor, these values returned to normal or were greatly diminished. Increased values were not found in hypertension presumably not due to pheochromocytoma. Lund[22] in studies of the epinephrine or nor-epinephrine content of venous blood reported an absence of these substances in normal subjects and in 7 patients with essential hypertension but detectable amounts of nor-epinephrine in 4 out of 5 patients in whom pheochromocytoma was found at operation. According to Lund the presence of 1/100 c.c. or more of epinephrine or nor-epinephrine in the venous blood is strongly suggestive of the presence of pheochromocytoma. Measurements of these substances in the blood and urine are difficult to perform technically, but preliminary data suggest that this test may prove useful in the diagnosis of pheochromocytoma.

Recently Goldenberg et al[23] have reported on the diagnosis of pheochromocytoma by evaluation of fluorometric measurements of urine extract, which reflect the total catecholamine content without specifying exact amounts of epinephrine and nor-epinephrine. These workers use a short method to screen out all cases giving a negative result for the presence of pheochromocytoma. If a positive test is obtained, a longer and more specific method is then required. In a series of 16 cases found to have pheochromocytoma at operation the use of these tests gave no false negative results. There were, moreover, no false positive tests in either normotensive patients or patients with essential hypertension so studied. It is worthy of note that in these 16 cases of proven pheochromocytoma, the benzodioxane test gave a false negative result in one out of 10 cases; regitine, a false negative response in one out of six patients; and histamine, a similar result in one out of eight cases.

Summary

1. *Benzodioxane Test.* The benzodioxane test is well standardized and is to be used in suspected cases of pheochromocytoma with sustained hypertension with the resting control blood pressure level greater than 150/110. There is a high incidence of false positive tests in patients with uremia, and such cases should not be subjected to the test. No sedatives or narcotics of any kind should be used for 24 hours prior to the test. Occasionally false negative tests occur and detract from the specificity of the test. Rarely there are alarming pressor responses in patients with essential hypertension when given benzodioxane, but no persistent damage has been known to occur. Mild side effects are quite common.

2. *Regitine Test.* This test is to be used only in patients with sustained hypertension or in whom the resting control blood pressure is greater than

150/110, that is to say, in cases in whom the benzodioxane test would be indicated. It is free of unpleasant side effects. As regitine does not produce the alarming rise in blood pressure that is sometimes encountered following benzodioxane administration, it is safer to use than benzodioxane in those patients with very high resting control blood pressures. Evaluation of the test both as to its standardization and reliability will have to await further experience with its use.

3. *Dibenamine Test.* The use of dibenamine as a diagnostic test for pheochromocytoma is to be discouraged as it gives too high an incidence of false positive results in patients with essential hypertension.

4. *Measurements of the Epinephrine and Norepinephrine Content of the Blood and Urine.* Preliminary observations with these tests are of extreme interest. It remains to be seen whether these findings may be more reliable in the diagnosis of pheochromocytoma than the pharmacological tests.

5. *Indications for Tests.* There can be little doubt that these pharmacological tests represent a distinct advance in the diagnosis of pheochromocytoma. In those patients with sustained hypertension who show none of the distinguishing clinical and laboratory features of adrenal medullary tumor, it becomes a matter of clinical judgment whether to employ these tests. It is our feeling that the tests should be used in most such instances of hypertension as well as in those cases in whom the diagnosis of pheochromocytoma is suspected on clinical grounds. If the positive diagnosis is made and if the tumor is removed by operation, the patient has an excellent chance of cure. It should be emphasized that none of the pharmacological tests are infallible. It may be necessary, therefore, to employ more than a single test to establish the diagnosis in a given instance.

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